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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER	
PURDY, KYLE A	

ART UNIT	PAPER NUMBER
1611	

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12/02/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/584,296	HAAS ET AL.	
	Examiner	Art Unit	
	Kyle Purdy	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-15 and 23-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5-15 and 23-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The Examiner acknowledges receipt of the amendments filed on 08/13/2009 wherein claims 1, 5-7, 14 and 26-28 have been amended and claim 4 has been cancelled.

2. Claims 1-3, 5-15 and 23-32 are presented for examination on the merits. The following rejections are made.

Response to Applicants' Arguments

3. Applicants arguments filed 08/13/2009 regarding the rejection of claims 1-11, 14, 15 and 23-30 made by the Examiner under 35 USC 102(e) over Haas (US 2006/0128736) have been fully considered and they are found persuasive. This rejection has been overcome in view of Applicants arguments.

4. Applicants arguments filed 08/13/2009 regarding the rejection of claim 4 made by the Examiner under 35 USC 103(e) over Burke (US5552156) in view of Perez-soler (US 5834012) and Allen (US 6316024) have been fully considered and they are found persuasive. This rejection has been overcome in view of Applicants cancellation of the claim.

5. Applicants arguments filed 08/13/2009 regarding the rejection of claim 1-3, 5-15 and 23-32 made by the Examiner under 35 USC 103(e) over Burke (US5552156) in view of Perez-Soler (US 5834012) and Allen (US 6316024) have been fully considered but they are not found persuasive.

6. The rejection of claims 1-3, 5-15 and 23-32 made by the examiner under 35 USC 103(a) is **MAINTAINED** for the reasons of record in the office action mailed on 02/26/2009.

7. In regards to the 103(a) rejection, Applicant asserts the following:

A) The liposomes of Burke are not cationic;

B) Perez does not teach that camptothecin (CPT) can self assemble with empty cationic nanoparticles;

C) Allen does not teach a self assembly method as is instantly claimed; And

D) One would not have been motivated to use CPT carboxylate because of its lower association with the liposomes and it's lower therapeutic activity.

8. In response to A, this argument is not found to persuasive. While the micelles of Burke may be neutral, one would have been motivated to formulate them such that they were cationic based on the teachings of the secondary references which state that cationic lipids are useful in CPT micelles as they help to stabilize and maintain the drug. Thus one would have been motivated to formulate the liposome such that it was cationic because in doing so would impart a stabilizing effect to the overall therapeutic micelle.

9. In response to B, Perez does not have to teach this limitation because the primary reference of Burke does. Perez is relied upon for providing the motivation to have CPT carboxylate containing micelle be cationic as well as providing the various species of cationic lipids for making the micelle such.

10. In response to C, Allen does not have to teach this limitation because the primary reference of Burke does. However, Allen does show the self-assembly process for a therapeutic targeting agent and preformed micelles which the Examiner believes would be similar to the kinetics of loading the micelle with CPT carboxylate; both have to penetrate the membrane of the micelle. Allen shows that the uptake of the targeting moiety by the micelle is time and temperature dependent. The longer the period of incubation, the greater the uptake of agent.

Thus, the notion of increasing the time the micelle is incubated with the therapeutic agent, i.e. CPT carboxylate, is quite obvious, and would have been an clear to any ordinarily skilled person because they would have expected the length of incubation to affect drug uptake.

11. In response to D, this is not persuasive. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or non-preferred embodiments. See MPEP 2123(II). Moreover, the use of patents as reference is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, and are relevant for all that they contain. See MPEP 2123(I). Thus, one would have been readily capable and motivated to use CPT carboxylate with a reasonable expectation for success in the successful loading and eventual treatment of a subject even if the carboxylate form is not as therapeutically active as the lactone form.

Maintained Rejections, of Record
Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

14. **Claims 1-3, 5-15 and 23-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burke et al. (US 5552156, published 09/03/1996; of record) in view of Perez-Soler et al. (US 5834012, published 11/10/1998) and Allen et al. (US 6316024, published 11/13/2001).**

15. Burke is directed to liposomal and micellar stabilization of camptothecin (CPT) drugs. Methods for making camptothecin loaded micelles are disclosed (see Examples 3 and 10). Example 3 teaches mixing preformed zwitterionic micelles (see instant claims 8 and 9) in a suspension with camptothecin solution (see instant claim 7) and giving the mixture time to equilibrate to form drug loaded micelles (see instant claims 1, 8 and 9). The mixture is aqueous (PBS) in nature (see instant claim 1). The micelles of Example 3 are made from dimyristoyl phosphatidylcholine (DMPC) which has a cationic ammonium head group and is amphipihlic (see instant claims 10 and 11). It is taught that camptothecin drugs bind the lipid bilayer membrane of the liposome and so it must be partially able to penetrate said membrane (see column 2, lines 10-15; see instant claim 1). The pH of the preparation is from between 3 and 7.4 (see Example 7 and lines 11-12; see instant claim 15). Moreover, formulations are disclosed where in CPT-carboxylate is used solely in the liposome.

16. Burke fails to include cationic lipids in the nanoparticle wherein the cationic lipid includes DOTAP or DMTAP. Moreover, Burke fails to teach that their method require a mixing time of between 10 minutes to 6 hours and an incubation temperature of between 4^{o}-25^{o}C.

17. Perez is directed to lipid complexed topoisomerase inhibitors (TII). An exemplified TII is camptothecin and its carboxylate salt (see column 3, lines 25-30). The lipids used to carry the

TII includes cationic lipids (see column 4, lines 55-65) such as SOTAP, DOTMA and DODAP (see instant claims 1 and 30). It's taught that cationic lipids such as these assist in complexing and maintaining the stability of the encapsulated compounds. The ratio of lipid to drug is to be from 150:1 to 5:1 (see column 4, lines 45-50; see instant claims 3 and 23-25).

18. Allen is directed to therapeutic lipsome compositions and methods of making said compositions. The method of making the active liposomes requires preforming the liposomes which may comprise cationic lipids such as DOTAP (see column 6, lines 15-30) and incubating said micelle with an active agent. Disclosed active agents include camptothecin and its analogs (see column 8, line 45). The method may performed various ways such as passive entrapment of the compound by hydrating the lipid film with the compound (i.e. self assembly) (see column 10, line 5). The method of loading the agent requires incubating at either 25 or 37°C and the time is varied from between 0-5 hours (see Example 1; see instant claims 12, 13, 31 and 32). It's shown that the longer the incubation time, the greater the loading efficiency of the agent to be encapsulated (see figs. 2A-2D).

19. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Burke, Perez and Allen with a reasonable expectation for success in arriving at a method of producing cationic micelles loaded with CPT-carboxyalte by a) providing an active agent; b; providing empty cationic nanoparticles; and c) incubating the active agent of a) with the nanoparticles of b) for a time sufficient to load the nanoparticles with the active agent wherein the loading process is a self-assembly process. With respect to the requirement that the CPT be under 4% lactone, this is implicit to the teaching of Burke because Burke teaches a micellar composition which has as its active agent CPT-

carboxylate. With respect to using a cationic lipid to form a cationic micelle, this is obvious. Perez teaches that cationic lipids are useful in CPT containing micelles because their inclusion helps to stabilize and maintain the drug. One would have been motivated to modify the teaching of Burke with such cationic lipids with a reasonable expectation in imparting a stabilizing effect for the encapsulated CPT drug. With respect to the incubation time and temperature, this is also obvious, especially in view of Allen. Both Burke and Perez are directed to making micellar CPT formulations but neither specifically disclose the instantly claimed temperature and time ranges. While it would have been obvious for any person of ordinary skill to optimize such parameters, Allen is relied upon to show that he instantly claimed ranges are commonly employed in the art for the loading of actives into micelles and are obvious. It's clear from Allen's teachings that time and temperature directly influence the fraction of active encapsulated by the liposome. Thus, it would have been obvious to any person of ordinary skill in the art to adjust and optimize the time and temperature of the incubation period such that the loading efficacy of the method could be sufficiently adjusted to allow for maximum loading efficiency of camptothecin into the micelles. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

Conclusion

20. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

21. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kyle A. Purdy whose telephone number is 571-270-3504. The examiner can normally be reached from 9AM to 5PM.

23. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau, can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

24. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Kyle Purdy/
Examiner, Art Unit 1611
December 1, 2009

/David J Blanchard/
Primary Examiner, Art Unit 1643